CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Fosetyl-Al
(Aluminum Tris (o-Ethylphosphonate)

Chemical Code 2210, Tolerance # 415
SB 950 # 135

November 7, 1997
Revised July 7, 1998, December 23, 1998

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, possible adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 165348 and 939060 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
Name: T981223
Prepared by J. Gee, 11/7/97, based on reviews by A. Apostolou and J. Gee; revised July 7, 1998 and December 23, 1998 by Gee.

Note: As of 1990, US EPA was not requiring any additional toxicology data.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 415-004, -005, -006, -007, -008 939030 - 939034** "Chronic toxicity (2 years) and carcinogenicity study in rats." (R. R. Trumbull, International Research and Development Corp. [IRDC], 347-016, 3/27/81) Fosetyl-Al , >95% purity, was fed in the diet to CD Sprague-Dawley rats, 80/sex/group, at 0 (diet), 2000, 8000 or 40,000/30,000 ppm for 24 months. [There were some problems with dietary levels in the first year - see Appendix III.] The high dose was reduced after 2 weeks based on clinical signs of urine staining of the abdomen, red coloration of the urine and lower body weight gain. Mean compound consumption was: M (0, 88, 348 and 1372 mg/kg/day) and F(0, 117, 450 and 1786 mg/kg/day). Ophthalmoscopic exams were done at 3, 12 and 24 months. Blood and urine samples were collected at 3, 6, 12, 18 and 24 months. There was no effect on body weight after the high dose was reduced. **Results:** No treatment-related effects on ophthalmology, hematology, or clinical chemistry were noted. The incidence of pheochromocytoma of the adrenal medulla was increased in treated males, controls through high dose (5/80, 7/79, 15/81* and 16/81**). Focal hyperplasia incidence (a morphological continuum with pheochromocytoma) of the adrenal medulla was 16/80, 18/79, 9/81 and 7/81. The combined incidence of pheochromocytoma and focal hyperplasia was similar for all groups, hence, the significance was questioned by the study pathologist and by A. Apostolou. Although the pheochromocytoma data are equivocal, DPR considers the apparent tumor increases to represent a treatment effect at this time, considering the pattern of incidence. For the urinary bladder, the effects were considered treatment-related in males at 30,000 ppm. Urinary bladder neoplasia (carcinoma and papilloma combined) was 1/78 for controls and 14/79** for high dose males. Transitional cell hyperplasia was also increased, being 1/78 in control group and 13/79 in the high dose group. **Possible adverse effects:** bladder neoplasia and pheochromocytomas in males**.** No similar findings were reported in female rats. The pathology slides were reread by a consulting pathologist with some notations such as "no discrepancies" and "Not present in section" (Appendix A). Chronic NOEL = 8000 ppm (urinary bladder findings in males). Study initially reviewed as unacceptable by A. Apostolou, 6/4/85 due to lack of dose justification. The study was re-classified as ACCEPTABLE at this time since the high dose gave a clear treatment response. One-liner by Gee, 4/24/97.

415-002 023490 One-page summary of 939030 - 034. No worksheet.

415-077 114842 Discussion of the oncogenic potential of fosetyl-Al. No worksheet.

415-077 114843 "3-Month oral toxicity study in the rat." (B. Coquet, IFREB, 10/7/77) Submitted as justification of the dose selection in the 2-year study in the rat. OFA rats (Sprague Dawley derived), 15/sex/dose level, were fed 0, 1000, 5000 or 25,000 ppm (equivalent to 75, 366 and 1922 mg/kg/day for males and 98, 481 or 2500 mg/kg/day for females) for 13 weeks. Purity was 99.8%. Hematology, clinical chemistry (including cholinesterases) and urinalyses were performed periodically. **Results:** There were no clinical signs at any dose. There were no effects on body weight or food consumption. Although there were some changes in hematology and clinical chemistry, none were consistent. The only effect reported was an increase in extramedullary hematopoiesis in the spleen of the high dose group. SUPPLEMENTAL STUDY. (Gee, 4/28/97). No worksheet.

415-003 939012 Duplicate of 114843.

415-018, -019, -020, -021, -022, -023, -024 939035 to 939041 "Lifetime chronic toxicity and carcinogenicity study in rats" (E. J. F. Spicer, study director, IRDC, 8/21/81) Test material was monosodium phosphite, containing 27% water, lot DA 117. Charles River CD rats were fed 0, 2000, 8000 or 32000 ppm (expressed as the anhydrous salt) for 27 months, 60/sex/group with 10/sex/group sacrificed at 12 months. Diets were examined periodically for content and homogeneity. Mean dose levels in males were 83.9, 347.6 and 1481.5 mg/kg and in females, 104.2, 434.1 and 1820.1 mg/kg/day. Ophthalmology, hematology, clinical chemistry and urinalyses were evaluated. **Results:** Body weights were decreased in high dose animals. There were sporadic differences in hematology, clinical chemistry or urinalysis but there was no consistent pattern identifying a treatment-related effect. Although there were slight increases in incidence of chronic nephritis in high dose males and females, this was not attributed to treatment by the pathologist. No evidence of an oncogenic effect. Acceptable as a SUPPLEMENTARY STUDY (test material not the active ingredient). (Apostolou, 6/10/85; Gee, 8/6/97).

CHRONIC TOXICITY, RAT

See under combined rat above.

CHRONIC TOXICITY, DOG

** 415-009, -077 939018, 114841 "Two year dietary toxicity study in dogs." (E. J. F. Spicer, International Research and Development Corporation [IRDC], 347-023, 10/19/81) Fosetyl-Al (lot DA 136, 96.9% [see 114841]), diet analyses indicated analytical concentrations were close to nominal doses) was fed in the diet at 0 (diet), 10,000, 20,000 or 40,000 ppm to 6/sex/group of beagle dogs for 24 months. Mean compound intake was 0, 309, 609, or 1228 mg/kg/day for males and 0, 288, 632 or 1190 mg/kg/day for females. Hematology, clinical chemistry and urinalyses were conducted pretest and at 1, 2, 3, 4, 5, 6, 12, 18 and 24 months. Ophthalmoscopic examinations were performed pretest and at 3, 6, 12, 18 and 24 months. Cholinesterase activity was measured at terminal sacrifice. **Results:** The incidence of "parts of stool covered with grey elastic-like material" was increased at 40,000 ppm but was noted in all treatment groups beginning at one year. Analysis of the feces indicated the material was not the test article but an "unknown" substance. There were no consistently significant effects on body weight, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, or urinalysis. Adequate parameters were measured. Histopathological examination indicated an increase in the incidence of seminiferous tubule degeneration in treated males (0/6, 0/6, 2/5 and 6/6, with increasing dose). The lesions consisted of the presence of spermatocytic and/or spermatidic giant cells in the lumen of the seminiferous tubules. Lesions were more numerous at 40,000 ppm than at 20,000 ppm with the same degree of severity. In females, there was a slight increase in the incidence and severity of vacuolar tubular lesions of the kidney (5/6, 4/6, 5/6 and 6/6 with increasing dose). NOEL = 10,000 ppm (testicular effects at 20,000 and 40,000 ppm in males). Originally reviewed as unacceptable due to major variances noted as dose selection with no overt toxicity at the high dose, no purity stated and no identification of grey feces (Apostolou, 6/5/85). Re-evaluation notes that diet analyses were adequately performed with concentrations being close to nominal, purity information has been submitted [-077, 114841], the high dose was equivalent to greater than 1000 mg/kg/day and the feces were analyzed for test article and found negative. Study is considered ACCEPTABLE at this time with no adverse effect. (Gee, 4/25/97)

415-002 23489 One-page summary of 415-009, 939018. No worksheet.

SUBCHRONIC, DOG

** 415-003 939013 "LS 74783 (aluminium ethylphosphite) 3 month oral toxicity study in the dog." (B. Coquet and M. Clair, translated by D. W. Long, I. F. R. E. B., 10/4/77) Fosetyl-Al (LS 74-783, batch DA 67, 99.7%) was fed in the diet to beagle dogs, 5/sex/group, at 0, 2000, 10000 or 50,000 ppm for 3 months. Mean intake was 58, 274 and 1309 mg/kg/day for males and 58, 272 and 1446 mg/kg/day for females. Actual doses were close to nominal. Food and water consumption, body weight, ophthalmology, rectal temperature, hematology, clinical chemistry including cholinesterase in the brain, and urinalysis were evaluated. After 13 weeks, the animals were fasted and killed. A number of organs were weighed and tissues examined for histopathology. There were no effects on any of the parameters measured or on histopathology. The apparent NOEL = 50,000 ppm. No worksheet. Acceptable study. (Gee, 8/7/97)

ONCOGENICITY, RAT

See under combined rat.

ONCOGENICITY, MOUSE

** 415-010, -011, -012, -013, -002, -077 939021, 939022, 939023, 939024, 939019 "24-Month carcinogenicity study in mice." (E. J. F. Spicer, International Research and Development Corporation [IRDC], 347-021, 8/11/81) Fosetyl-Al, lot DA 136, 96.9% purity, was fed in the diet to CD-1 mice, 60/sex/group, at 0 (diet), 2500, 10,000 or 20,000/30,000 ppm. The high dose was increased from 20,000 to 30,000 ppm at week 19. Mean compound consumption was 352, 1409 and 3956 mg/kg/day for males with increasing dose and 409, 1672 and 4550 mg/kg/day for females. Hematology was conducted at 12 months and at termination. Clinical chemistry and urinalysis were evaluated at termination. Body weight was slightly lower at the high dose in both sexes. No evidence for an oncogenic effect. NOEL = 30,000 ppm. Originally evaluated as unacceptable based on no evidence of toxicity at the high dose and no organ weights (Apostolou, 6/5/85). Re-evaluation in conjunction with the rebuttal submission in 415-077 finds the study to be ACCEPTABLE based on adequacy of the high dose. (Gee, 4/28/97).

415-077 Rebuttal to review of 939021 in 1985.

415-002 939019 Summary of above study. No worksheet.

REPRODUCTION, RAT

** 415-016 939029 "Effect of LS 74-783 on reproductive function of multiple generations in the rat" (Palmer, A. K. *et. al.*, Huntingdon Research Centre, 1/22/81) Fosetyl-Al, Batch DA 73 (97.3%), was fed in the diet at 0, 6000, 12000 or 24000 ppm to 25/sex CFY strain rats in the F0 generation. Diets were prepared weekly and analyzed for concentration every 13th week. F0 animals were maintained on test diet for 90 days before mating at 1:1 for a period of 20 days. The F1A pups were sacrificed at weaning and subjected to necropsy. Different pairs were mated for the F1B litters. Five females were killed on day 20 for teratological examination, day 0 being day dams were sperm positive in vaginal smears or a vaginal plug found. Twenty-five males and females of the F1B were selected to be raised to adults. After at least 90 days, they were mated for the F2A generation. Adults were remated for the F2B generation. Ten

pregnant F1B adults were sacrificed for teratological examination and the remainder allowed to rear F2B litters. Twenty-seven males and 39 females of the F2B litters were selected with 15/sex being reared on diets for at least 90 days when they were given a detailed macroscopic examination and tissues retained for possible microscopic examination. The remaining 12 males and 24 females were fed diets for 91 days, then mated twice for the F3A and F3B litters. Mating was 1 male:2 females. Ten male and 10 female pups of the F3B litters were selected for organ weights and histopathology. Note: Pups were selected to be raised to adults on the basis of body weights being closest to median weight. **Results:** Intake of test material was considerably higher for the F1B and F2B generations raised to adults than for the F0 in mg/kg bodyweight/day [younger when started on test diets]. There were 7 mortalities in males at 24,000 ppm in the F1B generation and 3 in the F2B. Autopsy showed changes in the urinary tract (hemorrhage of the bladder wall, increased renal pelvic dilatation, interstitial nephritis and papillary necrosis). Sporadic mortality occurred in other groups. Bodyweight gain was lower at 24000 ppm in both sexes, especially in the F1B and F2B males. For the F3B animals examined microscopically, 8/10 males and 8/10 females at 24000 ppm showed changes which included minimal epithelial hyperplasia and/or hypertrophy of the transitional epithelium, sometimes associated with small papillary projections and/or desquamation of epithelial cells in the lumen. Although tissues were saved from non-mated F2B animals, they were not examined. No adult breeders were examined for histopathology (a serious deficiency). No effects on reproductive parameters were reported. Parental NOEL = 6000 ppm (body weight, urinary tract changes). Pup NOEL = 12000 ppm (reduced body weight gain during lactation). Reproductive NOEL = 24000 ppm (no effects). Reviewed as ACCEPTABLE (Apostolou, 6/7/85). Re-examined by Gee, 7/24/97. Note: The lack of histopathology on the adult breeders is a serious deficiency but not adequate to reverse the initial evaluation in view of the completeness of the remainder of the study.

TERATOLOGY, RAT

** 415-016, -102 939028, 165348 “Effect of LS74-783 on pregnancy in the rat.” (A. K. Palmer and R. W. James, Huntingdon Research Centre, June 23, 1977, supplement dated 11/10/98 by L. J. Helfant) Fosetyl-Al, lot 794/795 FT, >98%, was given by gavage to CFY rats, 20/group, at 0 (sterile distilled water), 500, 1000 or 4000 mg/kg, days 6 to 15 of gestation. Dosing volume was calculated on day 6 and adjusted days 10 and 14. At 4000 mg/kg, 5/20 rats died or were sacrificed days 9, 10 and 11. Occasional mortalities were seen in the other groups due to dosing errors. Maternal weight gain was retarded the first four days of dosing with the controls gaining 23 g and the high dose, 3 g. The numbers of animals with viable young were 19, 18, 17 and 14 in control through high dose groups. One female at 4000 mg/kg had total litter resorption. Maternal NOEL = 1000 mg/kg (mortality, retarded weight gain the first 4 days of dosing). Developmental NOEL = 1000 mg/kg (effects considered secondary to maternal toxicity). Reviewed as unacceptable but upgradeable. (no analysis of dosing solutions). No adverse developmental effects. (Apostolou, 6/7/85; Gee, 8/4/97) Record No. 165348 contains a retrospective analysis of dosing solutions and stability over 24 hours. With the submission of the analytical data, the study was upgraded to ACCEPTABLE. (Gee, 12/23/98)

415-077 Rebuttal to 939028.

415-101 161149 Rebuttal dated April 30, 1998, indicating that a retrospective analysis of dosing solutions prepared as in the original study would be conducted if this would address the deficiency in 939028. See Response, dated July 7, 1998. (Gee, 7/3/98)

TERATOLOGY, RABBIT

** 415-016 939026 "Compound LS 74-783. Oral teratogenicity study in the rabbit." (J. Pasquet and R. Le Bail, translated by B. E. Sanderson, Centre Nicolas Grillet, France, December 6, 1976) Fosetyl-Al, batch FT 795, >98%, was given by gavage to female New Zealand White rabbits at 0 (10% aqueous gum arabic), 125, 250 or 500 mg/kg, 5 ml/kg body weight, days 6 - 16 of gestation. There were 12, 15, 15 and 14 pregnant rabbits in the control through high dose groups. There were no developmental effects reported. Evaluated as unacceptable (dose selection not justified with only minor effects on food consumption at the high dose). (Apostolou, 6/7/85; Gee 8/4/97) The study was re-evaluated, as indicated in the response dated July 6, 1998, and upgraded to ACCEPTABLE status. See response dated December 23, 1998. (Gee, 12/23/98).

415-101 161150 Rebuttal regarding the dose selection for 939026. The rebuttal contained comments on maternal body weight and the high dose versus the present "limit" dose. See response dated July 6, 1998. (Gee, 7/3/98)

GENOTOXICITY

Note: No one study on file for genotoxicity is adequate. There are, however, a number of studies with different endpoints. Therefore, the collective data from the studies indicate that fosetyl-Al was not mutagenic in the several systems in which it has been tested. No further studies are needed at this time. Gee, 8/11/97.

GENE MUTATION

415-017 939043 "Phosphorous acid, monosodium (37934 R. P., monosodium salt). Determination of mutagenic activity in *Salmonella typhimurium*." (F. Benazet and J. R. Cartier, translation by A. Salem, Centre Nicolas Grillet, December 28, 1977) 37934 R. P., metabolite, was tested with *Salmonella* strains TA1535, TA1537, TA98 and TA100 without activation at 0, 1, 100 and 1000 ug/plate in triplicate plates. In a repeat assay with and without rat liver activation, concentrations were 0, 125, 250, 500 or 1000 ug/plate, in triplicate. No increase in reversion rate. Positive control with activation with TA98 only. UNACCEPTABLE (inadequate positive controls with activation, no toxicity at the high concentration, not the active ingredient) Not upgradeable. (Apostolou, 6/10/85; Gee, 8/4/97)

415-015 939045 "Mutagenic activity of LS74,783 (32,545 R. P.) In *Salmonella typhimurium*." (A. Benazet and M. Cartier, Rhone-Poulenc, 7/29/77) LS 74,783 (no purity given, batch DEZ 943) was tested without liver activation at 0, 1, 10, 100 or 1000 ug/plate in trial 1 and at 0, 125, 250, 500 or 1000 ug in trial 2 with *Salmonella* strains TA1535, TA1537, TA100 and TA98. With activation in a single trial, 0, 125, 250, 500 or 1000 ug/plate were tested. Triplicate plates in each trial. In addition, a spot test was performed with and without rat liver activation. No evidence of a mutagenic effect under the conditions of the assays. Data reported as the average from the three plates. UNACCEPTABLE (no justification for highest concentration, no purity, inadequate positive controls with activation). Not upgradeable. (Apostolou, 6/6/85; Gee, 4/28/97)

415-076 114834 Duplicate of 939045.

415-015 030542 "Ames test (Salmonella typhimurium)." (D. H. Bouanchaud and J.-R. Cartier, Rhone-Poulenc, 11/20/81) Fosetyl-Al, lot DA 67, 99.7%, was tested with *Salmonella* strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation at 0 (distilled water), 125, 250, 500 or 1000 ug/plate, 3 plates per concentration. No increase in revertants. UNACCEPTABLE (inadequate positive controls with activation, inadequate

justification for the high concentration). (Apostolou, 6/6/85; Gee, 7/23/97)

415-076 114835 Duplicate of 030542.

415-028 939054 "Fosetyl-Al (32 545 R. P., aluminum salt) Aliette (wettable powder containing 80% fosetyl-Al), formulation EXP 1 659 B; *in vitro* mutagenesis in microorganisms" (D. H. Bouanchaud and J.-R. Cartier, Rhone-Poulenc, Centre Nicolas Grillet, December 9, 1981) *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to 125, 250, 500 or 1000 ug/plate, triplicate plates, with and without activation. The test material was 80% fosetyl-Al, batch 81-1. Concentrations were expressed as fosetyl-Al. At 1000 ug/plate, there was slight inhibition of bacterial growth. No increase in reversion rate. UNACCEPTABLE (positive control with activation with TA98 only, inadequate justification for high concentration). (Apostolou, 6/11/85; Gee, 8/4/97)

415-076 114836 Duplicate of 939054.

CHROMOSOME EFFECTS

415-015 939047 "Investigation of the possible mutagenic activity of 'Aliette' and of hydrated monosodium phosphite." (G. Siou, C.E.R.T.I., 12/23/77) Fosetyl-Al (Batch DA 67, >97%) and hydrated monosodium phosphite (Batch OP 77,051, 97%) were given by oral gavage to male Swiss mice. 'Aliette' was given at 1, 2 or 4 g/kg to 10, 10 and 5 mice per group in two doses 24 hours apart. All 5 mice at 4 g/kg were dead after the second dosing. The phosphite was given at 1, 2, and 4 g/kg to 5, 5 and 10 male mice per group with increasing doses on the same schedule. Ten (10) mice served as controls. Polychromatic erythrocytes were scored for micronuclei 6 hours after the second dose with 2000 cells per animal from the bone marrow. UNACCEPTABLE (single harvest time, males only with no justification, not clear if concurrent positive controls). No evidence of an adverse effect. (Apostolou, 6/6/85 and Gee, 4/29/97)

415-076 114838 Duplicate of 939047.

415-015 939050 "Fosetyl-Al (32 545 R.P., aluminum salt). Micronucleus test in the mouse by the oral route." (A. Cordier and E. Fournier, Centre Nicolas Grillet, 11/24/81) CD-1 mice, 5/sex/dose group, were given 0.6, 1.2, 2.4 or 3.6 g/kg by oral gavage as a single dose with sacrifice after 30 hours or as 2 doses 24 hours apart with sacrifice 48 hours after the first dosing with fosetyl-Al, lot DA 203 (97.5% purity). All animals given 3.6 g/kg died and 10% of those given a single dose of 2.4 g/kg died. A total of 8000 cells per dose group were scored for micronuclei in polychromatic erythrocytes and for cytotoxicity. Individual data were included in the report. The positive control, triethylenemelamine (TEM), was from an assay run immediately after the fosetyl-Al test using the same protocol. No evidence of induction of micronuclei formation was reported. UNACCEPTABLE (sampling times). (Apostolou, 6/6/85; Gee, 4/29/97).

415-028 939051 "Fosetyl-Al (32 545 R. P.). Aliette formulation EXP 1659-B (wettable powder containing 80% fosetyl-Al). Micronucleus test in the mouse by the oral route" (A. Cordier and E. Fournier, Rhone-Poulenc, Centre Nicolas Grillet, December 14, 1981) Aliette formulation EXP 1659-B, 80%, was given to groups of 5 CD1 mice/sex/dose at 0, 0.96, 1.92 or 2.88 g/kg active ingredient (1.2, 2.4 or 3.6 g/kg formulated product) in 10% aqueous solution of acacia. Two dosing regimens were used: a single oral dose and sacrifice after 30 hours or two doses 24 hours apart and sacrifice at 48 hours after the first dose [24 hours after the second dose]. 1000 polychromatic erythrocytes were scored per mouse, 4/sex/group being evaluated. No increase in the percentage of polychromatic erythrocytes with micronuclei. No concurrent positive control. Data from an earlier study with TEM were included in the report. Slight

evidence of cytotoxicity at 48 hours with the high dose. UNACCEPTABLE (no concurrent positive control, number of animals scored, sampling schedule) (Apostolou, 6/11/85; Gee, 8/4/97)

425-076 114840 Duplicate of 939051.

DNA DAMAGE

415-015 939053 "Inductests on phosphorous acid and LS 74,783." (A. Salem, translator, Institute Pasteur, Paris, ½/78) Fosetyl-Al, 99.7%, and phosphorous acid were tested with *Escherichia coli* K12 for the induction of ? phage from prophage state at up to 2 mg/plate. Following induction, the bacteriophages were released and plaques formed in the indicator strain. The number of plaques was related to the amount of test material in the plate. The quantity causing induction of ½ the maximum was determined. The test was run with and without activation using both plates and pre-incubation in liquid medium. The strains of bacteria were GY 4015 as indicator, GY 5027 as measure of inducer activity (lysogenic for phage ?) and GY 5029 as a measure of toxicity. Fosetyl-Al at >50 ug/plate inhibited phage development without activation. One-half maximum induction with activation was > 2 mg. No inducing activity was detected. Evaluated as having insufficient information. UNACCEPTABLE (results in graphic form only) (Apostolou, 6/7/85; Gee, 7/23/97).

415-076 114837 Duplicate of 939053.

415-015 030541 "Induct-test (E. Coli K 12, strain GY 5057)." (D. H. Bouanchaud and J.-R. Cartier, Rhone-Poulenc, 11/20/81) Fosetyl-Al, lot D 67, 99.7%, was tested with *E. coli* with and without rat liver activation for the induction of prophage ? at 0, 0.5, 1, 10, 50, 100 or 200 ug/ml with lysogenic strain GY 5057 (10^3 bacteria) and using GY 4691 as the "neutral" strain (about 10^8 bacteria/ml). Incubation was in liquid medium for 20 minutes at 37°C followed by the addition of molten soft agar containing the indicator strain, GY 4015, sensitive to ? phage. Single plate per concentration. Plates were incubated for 18 hours. The lytic plaques were counted and the ratio of the induced lysogenic bacteria to the number treated was calculated as a measure of the inducing effect of the test material. Exposure to fosetyl-Al did not induce prophage. UNACCEPTABLE (single plate per concentration). (Apostolou, 6/6/85; Gee, 7/23/97)

415-076 114835 Duplicate of 030541.

415-028 939054 "Fosetyl-Al (32 545 R. P., aluminum salt) Aliette (wettable powder containing 80% fosetyl-Al), formulation EXP 1 659 B; *in vitro* mutagenesis in microorganisms. Induct-test (E. Coli K12, strain GY 5057 " (D. H. Bouanchaud and J.-R. Cartier, Centre Nicolas Grillet, December 9, 1981) *Escherichia coli* was incubated with Aliette at 0, 0.05, 0.1, 0.5, 1, 5, 10, 50, 100, 500 or 1000 ug/ml, single plate, with and without activation. No induction of ? prophage was reported. UNACCEPTABLE (single plate) (Apostolou, 6/11/85; Gee, 8/4/97)

425-076 114836 Duplicate of 939054.

415-015 030540 "Test in yeast (Saccharomyces cerevisiae D 7)" (D. H. Bouanchaud and J.-R. Cartier, Rhone-Poulenc, 11/20/81) Fosetyl-Al, lot D67, 99.7%, was tested with *Saccharomyces cerevisiae* without activation at 250, 500 and 1000 µg/ml (limit of solubility in buffer) and with rat liver activation at 125, 250 and 500 µg/ml, for 1 hour incubation. Three genetic events were examined: Conversion to l-tryptophan independence, reverse mutation to l-isoleucine independence and mitotic recombination to adenine requirement. EMS was the positive control. Treated cells were spread on agar plates with triplicates for convertants and 6

plates for revertants. Treatment was negative for all three genetic events. UNACCEPTABLE (inadequate number of plates for convertants). (Apostolou, 6/6/85; Gee, 7/23/97)

425-076 114835 Duplicate of 030540.

415-028 939054 "Test in yeast (*Saccharomyces cerevisiae* D7)" (D. H. Bouanchaud and J.-R. Cartier, Centre Nicolas Grillet, December 9, 1981) Yeast strain D7 was incubated with 80% Aliette wettable powder at 0, 125, 250 or 500 ug/ml (limit of solubility) for 1 hour with and without rat liver activation. Two trials were run. The frequency of tryptophan-independent convertants, isoleucine-independent revertants and recombinants with some degree of adenine requirement were determined. At 250 and 500 ug/ml, Aliette solutions were slightly cloudy. The only positive control was EMS with and without activation. No evidence of an effect of treatment. UNACCEPTABLE (inadequate positive control with activation). (Apostolou, 6/11/85; Gee, 8/4/97).

415-076 114836 Duplicate of 939054.

415-015 030539 "DNA repair test (E. coli)" (D. H. Bouanchaud and J.-R. Cartier, Rhone-Poulenc, 11/20/81) Fosetyl-Al, lot D67, 99.7%, was tested with *Escherichia coli* strains pol A^- (p 3478) and pol A^+ (W 3110) with and without rat liver activation in liquid culture for two hours. Concentrations without activation were 0 (DMSO), 12.5, 25, 50 or 100 µg/plate; with activation, 0 (DMSO), 6.25, 12.5, 25, 50 or 100 µg/plate. EMS was the positive control for both. Differential survival in terms of colonies per plate of the two strains were scored. There was no difference in the surviving colonies between the two strains. Treatment did not have an effect on DNA as measured by the DNA repair test. No adverse effect. No toxicity was noted in either strain. UNACCEPTABLE (too few plates (1) per concentration, no justification of the high concentration, inadequate positive controls) (Apostolou, 6/6/85; Gee, 7/23/97)

415-076 114835 Duplicate of 030539.

415-028 939054 "DNA repair test (*E. coli*)" (D. H. Bouanchaud and J.-R. Cartier, Centre Nicolas Grillet, December 9, 1981) *Escherichia coli* strains $polA^+$ and $polA^-$ were incubated in liquid medium for two hours with 0, 62.5, 125, 250 or 500 ug/plate (limit of solubility) of Aliette 80% fosetyl-Al before plating. No positive control with activation. One trial with and without rat liver activation. Duplicate plates. Negative for differential growth. No evidence of toxicity. UNACCEPTABLE (inadequate positive control). (Apostolou, 6/11/85; Gee, 8/4/97)

415-076 114836 Duplicate of 939054.

NEUROTOXICITY

Not required at this time.

SUPPLEMENTAL STUDIES

415-025 939057 "Aluminum ethyl phosphite (LS 74.783) excretion study in rats." (J. B. Unsworth, May & Baker, 9/1976) Aluminum ethyl-^{14}C phosphite was given to Sprague-Dawley rats, 3/sex, at 250 mg/kg/day for seven days in water. Urine, feces, exhaled air and tissues were evaluated. Recovery was evaluated on a daily and cumulative basis. Exhaled carbon dioxide was the major route with urine being second. Only a small amount was found in the feces and tissues with more in the liver and kidneys than the brain, spleen, lungs or heart. Totals of 98.94 and 96.19 percent were recovered in males and females, respectively. From the daily excretion patterns, the test article was excreted rapidly in both sexes. No worksheet.

SUPPLEMENTAL STUDY. (Gee, 8/6/97)

415-025 939058 "Aluminum ethyl phosphite (LS 74.783) metabolism study in rats." (J. B. Unsworth, May & Baker, 10/76) Metabolism of LS 74.783 labeled with ^{14}C was studied in male and female rats following a single daily dose of 250 mg/kg/day for 7 days. Metabolites were recovered from urine, feces and carcass. Samples were extracted with water and quantitated by liquid scintillation. Metabolites were separated by gas chromatography. LS 74.783 was recovered from urine as either unchanged compound or as phosphite, with more as phosphite. The same was found for feces, in much lower amounts. The conclusion was that metabolism is rapid and was excreted as phosphite before oxidation to phosphate. No worksheet. SUPPLEMENTARY STUDY. (Gee, 8/6/97)

415-025 939059 "Phosphorous-^{32}P acid excretion study in rats." (J. B. Unsworth, May & Baker, 7/77) The test material (sodium phosphite-^{32}P) was given in 7 daily doses to 3 Sprague-Dawley rats/sex at 111 mg phosphorous acid/kg/day. Excretion in urine and feces was followed over the seven days plus an additional 72 hours after the last dose. Radioactivity was quantitated by liquid scintillation. Blood and tissue samples were solubilized, then the radioactivity quantitated. The major portion of the ^{32}P was found in the urine with a lesser amount in the feces. Minor amounts of were found in the carcass 72 hours after the final dose. No worksheet. SUPPLEMENTARY STUDY. (Gee, 8/6/97)

415-025 939060 "Phosphorous-^{32}P acid metabolism study in rats." (J. B. Unsworth, May & Baker, 3/78) Phosphorous sodium salt, labeled with ^{32}P, was given to rats [see 939059 for details]. Metabolites were extracted with water from urine, feces and selected tissues and intestinal tract. Radioactivity was quantitated by liquid scintillation counting. Both thin-layer chromatography and gas-liquid chromatography were used to identify the metabolites. The major portion was excreted in the urine (59-65%) with 30-32% in the feces. In the urine, the major component was unchanged phosphite. In the feces, the major components were phosphite (usually >80%) and phosphate. There was inadequate recovery of radioactivity from tissues for analysis. No worksheet. SUPPLEMENTARY STUDY. (Gee, 8/7/97)

415-025 939011 "Monoethylphosphonic acid, aluminum salt (LS 74 783 = 32 545 R. P., aluminum salt). Effects in a number of pharmacological tests." (C. G. Caillard, et. al., 7/11/80) Five experiments were reported: effects on the nervous system of the mouse by i.p. route; effect on isolated guinea pig ileum; effects on cardiovascular and respiratory systems of the dog (and rabbit); effects on skeletal muscle of rabbit; and hemolytic and anticoagulant effects in the rabbit. Mouse: 5/sex were given i.p. doses of 31.25, 62.5, 125, 250 or 500 mg/kg. Mice were observed for up to 21 days. At 31.25, slight hypothermia was observed. At the higher doses, sedation was observed, increasing with dose. Guinea pig ileum: there was no effect of the test material on contractions. Cardiovascular and respiratory systems: Dog: no effects; rabbit: no effects. Skeletal muscle, rabbit: no effect on the contraction of the gastrocnemius muscle from electrical stimulation. Hemolytic and anticoagulant effects in rabbit: no hemolytic effects after doses of 5 or 10 mg/kg i.v. There was no increase in coagulation time after 5 or 10 mg/kg. No worksheet. SUPPLEMENTARY STUDY. (Gee, 8/7/97)

415-014 939056 "Fosetyl-Al (LS 74783). Determination of calcium and phosphorus in the serum, urine and faeces of the rat during one month's treatment with the compound mixed in the feed." (R. Kalifat et. al., Centre Nicolas Grillet, 1/29/81) Fosetyl-Al, 97.8%, dot DA 112, was fed to C.O.B.S. rats, 5/sex/dose, at 0, 10000, 20000 or 40000 ppm for 1 month (daily intake approximately 0.7, 1.5 and 3 g/kg). The calcium and phosphorus content of urine and feces of fasted rats was determined and histological examination of kidneys, thyroid and parathyroid performed. No mortality, effect on food consumption or body weight was reported. Serum levels of Ca and P were similar to controls. Calcinuria was reported, especially at the high dose in males but also at lower doses and in females. For phosphorus, there was a slight decrease

in the urine, especially for males at the high dose. An increase in excretion of phosphorus in the feces of males at the mid and high doses was found. There were no histological changes in the thyroid or parathyroid tissues. In the renal tubules of males, especially at the high dose, cells showed signs of vacuolar degeneration. At 20,000 ppm, results were similar but the number of cells affected were fewer. No worksheet. SUPPLEMENTARY STUDY. (Gee, 8/7/97)

21-DAY DERMAL STUDY IN THE RABBIT

415-003 939016 "The effect of repeated application of LS 74783 technical to the skin of rabbits for twenty-one days." (S. R. Kynoch et. al., Huntingdon Research Centre, 4/4/79) Fosetyl-Al (LS 74783, batch nos. DA112 and DA67, 97.8% and 99.7%), was applied to intact and abraded skin at 0 (distilled water), 0.38, 0.75 and 1.5 g/kg/day, 6 hours/day, for 21 days. Ten (10) per sex New Zealand White rabbits were treated per group. Approximately 10% of the body was exposed for dosing with 5/sex having intact skin and 5 abraded. A volume of 2.5 ml/kg/day was applied and covered with an impervious bandage for 6 hours followed by washing. Local dermal irritation was recorded daily. Hematology was performed. A limited number of tissues were examined microscopically: skin, liver and gall bladder, kidneys, abnormal tissues. Fifteen of 20 animals at 1.5 g/kg showed changes in the skin: acanthosis, hyperkeratosis and chronic inflammatory cell infiltration; 16/20 at 0.75 g/kg showed similar changes but to a lesser degree. The low dose and controls showed similar but much more minor changes. No other effects were reported for body weight, hematology, histopathology. Individual data are included. No worksheet. ACCEPTABLE STUDY. (Gee, 8/7/97)